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REMARKS/ARGUMENTS

This preliminary amendment is presented to place the application in better form for examination. No new matter has been added. Early examination and favorable consideration of the above-identified application is earnestly solicited.

The present application is a Request for Continued Examination (RCE) application of the immediately preceding parent application which itself was a Continuation of grandparent application No. 09/674,800, filed November 06, 2000.

In the Office Action mailed in the immediately preceding parent application on October 3, 2003, which was also the first Office Action in that RCE application, pending claims 16-31 were finally rejected pursuant to 35 U.S.C. 103 (a) as being unpatentable for obviousness. Specifically, claims 16-22 were rejected over U.S. Patent 5,985,915 to Frangin et al ("Frangin"); claims 16, 17, and 19-22 were rejected over U.S. Patent 5,616,591 to Poss ("Poss"), in view of Frangin; and claims 22-31 were rejected over Poss and Frangin, in view of U.S. Patent 5,464,628 to Jalonen et al ("Jalonen").

Applicants respectfully disagree with the foregoing bases for rejection of the claims previously in the case; and reiterate and reassert the arguments previously made with regard to distinguishing the subject matter of the present invention, as recited in the claims, from those references.

Additionally, Applicants make the following further remarks and arguments distinguishing the subject matter of the present invention as recited in claims 32-43, newly submitted with the present RCE application.

Frangin discloses the use of certain benzofuran derivative compounds, particularly amiodarone, dronedarone, and desethylamiodarone, and their salts, having antiarrhythmic activity,

for the treatment of cardiovascular disease. The use of these compounds, together with a pharmaceutically acceptable vehicle is disclosed (see, e.g., col. 6, lines 50-61) and claimed (see, e.g., claim 1). In certain specific alternative embodiments of Frangin, the further simultaneous or sequential administration of an additional cardioactive agent is disclosed (see, e.g., col. 8, line 34 - col. 9, line 38) and claimed (see, e.g., claims 23 - 25). Frangin also discloses, at col. 6, lines 24 - 28 (which occurs before the further disclosure of the embodiment having a further, second active agent associated with the principal benzofuran derivative agent) that the "pharmaceutical compositions" (again apparently referring to the benzofuran derivatives, i.e., the principal active ingredient, referred to in the preceding paragraph at col. 6, lines 21 - 23) may be provided in any form (with "transdermal" being specifically included and recited; see col. 6, line 27) for administration to humans. In the paragraph ending at col. 6, lines 33 - 36, reference is made to an administerable unit (again, understood to mean of the principal active agent, i.e., benzofuran derivative) including a device called a "patch" for transdermal administration.

It is only subsequently, at col. 8, lines 66 - 67, in the discussion of administration of the principal benzofuran derivative agent simultaneously or sequentially associated with at least one additional cardioactive agent, that angiotensin II inhibitors, specifically including candesartan, are mentioned.

It is respectfully submitted that Frangin does not provide enabling disclosure to teach administration of even the principal active agent (benzofuran derivative) via a transdermal "patch" delivery system in that it does not provide enabling disclosure as to the type and construction of such a patch that could be utilized for the delivery of the benzofuran derivative. Claim 1 of Frangin merely recites "in combination with one or more pharmaceutically acceptable vehicles". Claim 14 recites administration by the transdermal route, which thus presumably refers to via a "patch" type

device, because "topical", presumably referring to via an ointment or cream for example, is listed as a separate delivery route in claim 14. According to an interpretation most favorable to Frangin, the appropriate "pharmaceutically acceptable vehicle" for the transdermal route, meaning via a "patch" type device, rather than via a topical cream or ointment, might be thought to include the "patch" itself or the materials out of which a "patch" were constructed. Although the list of appropriate pharmaceutical excipients or vehicles recited at col. 6, lines 58 - 61, is only exemplary, it should be pointed out that that listing does not include a transdermal patch per se or materials from which same would be constructed, but rather only includes compounds and substances typically associated with other delivery routs, e.g., oral, parenteral, sublingual, and topical. Because nothing in the specification explicitly refers to the administration via the transdermal "patch" delivery route of the embodiment incorporating the principal benzofuran derivative active agent associated with a second active agent, such as an angiotensin II inhibitor, e.g., candesartan; and because claims 23 - 25 (drawn to the embodiment incorporating a second active agent) do not include the limitations of claim 14 (reciting the transdermal delivery route), applicants respectfully submit that Frangin does not teach or disclose, and at most only inferentially suggests, that candesartan is capable of delivery by a transdermal "patch" delivery route, and then, only when in combination with a benzofuran derivative active agent, not by itself.

Accordingly, it is respectfully submitted that the 35 U.S.C. 103(a) obviousness rejection of the claims of the present application is improper and should be withdrawn, and that new claims 32-43, submitted hereinabove, patentably distinguish over Frangin.

Poss discloses certain indole and benzimidazole-substituted quinoline derivatives, which are angiotensin II inhibitors; and that the disclosed compounds are capable of administration by transdermal patches (see col. 8, lines 19 - 23). Poss does not disclose or even mention candesartan,

which although an angiotensin II inhibitor, is not, in any case, one of the class of indole and benzimidazole-substituted quinoline derivative compounds disclosed by Poss. Therefore, there is nothing in Poss that teaches, discloses, or even remotely suggests that candesartan is capable of delivery by a transdermal "patch" type delivery mechanism or route. A person of ordinary skill in the art would recognize that although candesartan is an angiotensin II inhibitor, it has a different structural formula and properties from the compounds of Poss, so that just because Poss states that the compounds it discloses are capable of administration by a transdermal "patch", that does not mean that all angiotensin II inhibitors, especially those with different structure and properties, such as candesartan, are similarly capable of delivery by that route. In fact, applicants state in the present application at page 3, lines 9 - 13, that "it has now been found, **surprisingly** [emphasis supplied], that candesartan and/or its pharmaceutically suitable esters and salts can be administered by means of a transdermal therapeutic system in such a way that a therapeutically effective blood level is reached", thereby indicating that according to the prior art, it was thought that candesartan was incapable of being effectively delivered by a transdermal route.

Accordingly, it is respectfully submitted that the 35 U.S.C. 103 (a) rejection of claims of the present application as being obvious over Poss in view of Frangin is inappropriate and should be withdrawn; and it is further respectfully submitted that the new claims in the present application, submitted hereinabove, patentably distinguish over Poss, either taken alone or in the Examiner's proffered combination with Frangin.

Jalonen discloses certain pharmaceutical compositions containing 4-substituted imidazoles, that are capable of being administered transdermally, which, according to the reference, includes in the form of an ointment, emulsion, gel, lotion, solution or cream (i.e., what is generally referred to as "topically", and what is thought to be encompassed by the use of the term "topical" in Frangin,

discussed above); as well as by one of the three delivery systems (i.e., "patch" type systems) disclosed in Jalonen.

As with Poss, discussed above, Jalonen does not disclose or even mention candesartan, which, in any case, is not one of the class of 4-substituted imidazole compounds disclosed by Jalonen. Candesartan, as disclosed in the specification of the present application at page 1, second paragraph, is (2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid). The structural formula of candesartan is illustrated in the accompanying illustration obtained from the website of Tianyo Pharmaceutical & Chemical Co., Ltd (http://www.tianyuchem.com/product001.htm), upon a search under the name candesartan. As can be seen, the structure of candesartan is different from the structure of the compounds in Jalonen, as shown by formulae I and II of that reference. Candesartan a carboxylic acid-substituted benzyl group attached to the imidazole group, which is not present in the compounds of Jalonen. Therefore, there is nothing in Jalonen that teaches, discloses, or even remotely suggests that candesartan is capable of delivery by a transdermal "patch" type delivery mechanism or route. The compounds of Jalonen are disclosed to be α_2 - adrenoceptor active agents, not angiotensin II inhibitors, although certain particular substituted compounds of the formulae disclosed in Jalonen are said to have, *inter alia*, antihypertensive effects (see, e.g., col. 1, lines 36 -66). A person of ordinary skill in the art would recognize from the fact that because candesartan has a different structural formula and properties from the compounds of Jalonen, just because Jalonen states that the compounds it discloses are capable of administration by a transdermal "patch", that does not mean that all compounds having antihypertensive effects, nor even all imidazoles, especially those with different structure and properties, such as candesartan (with, at least, its additional carboxylic acid-substituted benzyl group, which affects its molecular weight, its stereochemistry, and hence its transdermal

absorbability), are similarly capable of delivery by that route. It is again emphasized to the Examiner that applicants state in the present application at page 3, lines 9 - 13, that "it has now been found, **surprisingly** [emphasis supplied], that candesartan and/or its pharmaceutically suitable esters and salts can be administered by means of a transdermal therapeutic system in such a way that a therapeutically effective blood level is reached", thereby indicating that according to the prior art, it was thought that candesartan was incapable of being effectively delivered by a transdermal route. The differences in structural formula between the ester of candesartan (candesartan cilexetil) and the compounds of the structural formulae I and II of Jalonen is seen from the attached sheet showing the structural formula of candesartan cilexetil, also obtained from the website of Tianyu Pharmaceutical & Chemical Co., Ltd, at (http://www.tianyuchem.com/product002.htm).

Accordingly, it is respectfully submitted that the 35 U.S.C. 103 (a) rejection of claims of the present application as being obvious over Poss and Frangin, in view of Jalonen, is inappropriate and should be withdrawn; and it is further respectfully submitted that the new claims in the present application, submitted hereinabove, patentably distinguish over Jalonen, either taken alone or in the Examiner's proffered combination with Poss and Frangin, or with either of those individually.

For the foregoing reasons, it is respectfully submitted that new claims 32-43 of the present RCE application are not obvious over, and patentably distinguish over, Frangin, Poss and Jalonen, taken individually and in any combination. It is respectfully requested that the Examiner enter this Preliminary Amendment, and, it is submitted, that after examination of the present RCE application in view of the claims presented hereinabove and the accompanying arguments and remarks distinguishing and overcoming the references previously applied in the case, the Examiner will find that claims 32-43 of the present application are in-condition-for-allowance, the early notification of which is earnestly solicited.

Any additional fees or charges required at this time in connection with the application may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,

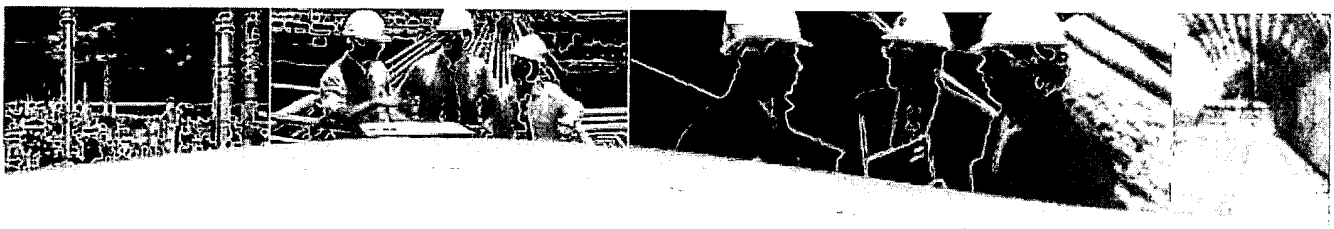
COHEN, PONTANI, LIEBERMAN & PAVANE

By Howard R. Jaeger

Howard R. Jaeger
Reg. No. 31,376
551 Fifth Avenue, Suite 1210
New York, N.Y. 10176
(212) 687-2770

December 31, 2003

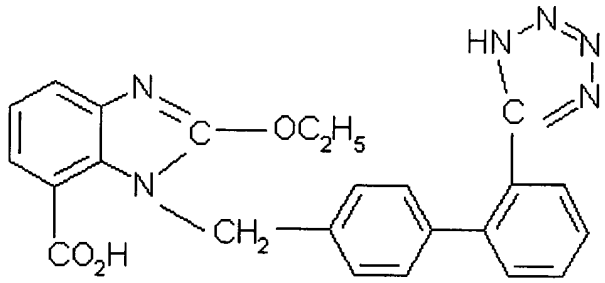
天宇医药化工
TIANYU PHARMACEUTICAL & CHEMICAL CO.,LTD.



Products

Candesartan

Structural Formula:



Molecular Formula: $C_{24}H_{20}N_6O_3$

Molecular Weight: 440.46

CAS: 139481-59-7

Specifications Further Q/TY 06-2001 specification customizable upon request.

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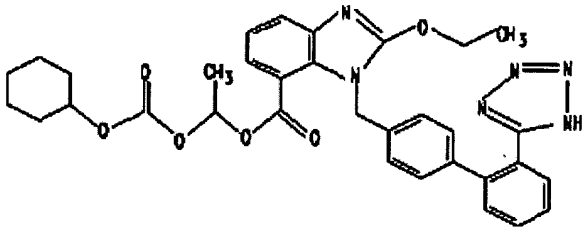
TIANYU PHARMACEUTICAL & CHEMICAL CO.,LTD.

Products

Candesartan Cilexetil

Structural Formula:



Molecular Formula:	$C_{33}H_{34}N_6O_6$
Molecular Weight:	610.67
CAS:	145040-37-5

Specifications Further Q/TY 10-2003 specification customizable upon request.